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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,711	PROCKOP ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 20 October 2004 has been entered.

Applicant's response and amendments of 20 October 2004 have been entered.

Claims 1, 5, 9, and 13-16 are currently amended.

Claims 17-32 are newly added.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 18-20, 22, 24, and 26-28 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 2-4, 6, 8, and 10-12, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a

substantial duplicate of the allowed claim. See MPEP § 706.03(k). However, for purposes of compact prosecution, these claims have been also rejected according to the claims from which they depend.

Claim Rejections - 35 USC § 112, new matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18-20, 22, 24, and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's claims have been amended to encompass cultured marrow stromal cells that are primary cultured cells. Applicant also admits that there exists no support in the specification for such term as "primary" (Applicant's response of 20 October 2004, pp. 7-8, paragraph bridging). Hence, this new matter rejection is held.

Response to Arguments – New Matter

Applicant's arguments of 20 October 2004 have been fully considered but are not found persuasive.

Applicant argues that although the term "primary cultured cells" is not expressly supplied by the specification, the Artisan would be able to infer based upon the disclosure of the

Application, that the cells of the invention are primary cultured cells (Applicant's response of 20 October 2004, pp. 7-8, paragraph bridging).

Such argument is not persuasive. The test is not whether the cells of the invention are primary cultured cells, but whether Applicant has sufficiently demonstrated that they have the possession of the invention now claimed at the time of invention by Applicant. Moreover, it is still unclear after Applicant's explanation whether, *inter alia*, such "primary cultured cells" are primary because they are derived from an organism, whether they are "primary cultured cells" because they are able to increase hematopoeisis, whether they are "primary cultured cells" because they are not modified in any way, e.g., transformed, or whether they are "primary cultured cells" because of the conditions of culturing.

Applicant argues that, as set forth in MPEP 2163, there is no *in haec verba* requirement for claim limitations, and that the specification adequately supports "a primary cultured cell" (Applicant's response of 20 October 2004, p. 8, paragraph 2).

Such is not persuasive. Applicant may have support for a marrow stromal cell, isolated from bone marrow cells, and cultured under specific conditions, but due to the aforementioned ambiguities (Supra, two paragraphs above), Applicant certainly does not have support for the genera of primary cultured marrow stromal cells, as the Artisan could not interpret what was meant by such primary cultured cells from Applicant's specification.

Applicant argues that the primary cultured cells of the specification would not be transformed by any vector nor encompass immortalized cells, because Applicant has not specifically demonstrated the marrow stromal cells to be so transformed or immortalized (Applicant's response of 20 October 2004, p. 8, paragraph 2).

Such is not persuasive. Applicant's argument itself is inconsonant with the same arguments to having adequate description of the primary cultured cells themselves. Applicant argues that even though they do not disclose primary cultured cells, they have possession of the cells through a single species; yet, because they do not disclose such cells are transformed or immortalized, that they specifically describe that such cells would not be so transformed or immortalized. The argument is not considered persuasive.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-6, 8-10, and 12-16 remain rejected, and Claims 18, 20, 22, 24, 26, and 28 are rejected for reasons necessitated by the amendments, under 35 U.S.C. 102(b) as being anticipated by Anklesaria, et al. "Engraftment of a clonal bone marrow stromal cell line *in vivo* stimulates hematopoetic recovery from total body irradiation" (1987) Proc. Natl. Acad. Sci., USA, 84: 7681-85, hereinafter referred as "Anklesaria '87" for reasons of record in the previous Office Actions of 6 October 2003 and 19 May 2004.

Applicant has amended the claims to limit the cultured marrow stromal cells to primary cultured cells.

Response to Arguments

Applicant's arguments filed 20 October 2004 have been fully considered but they are not persuasive.

Applicant argues that Ankelsaria, in using cells that have been transformed with the neomycin resistance gene, and being a clonal cell line, are not the "primary cultured cells" of

Applicant's claims (Applicant's arguments of 20 October 2004, p. 9, paragraph 4-p. 10, paragraph 1).

This argument is not persuasive because the claims encompass these cells, which were isolated from a mammal, and the cells are cultured *in vitro* prior to transplantation. Moreover, such cells used by Ankelsaria are primary cells that have been cultured, as they are marrow stromal cells (e.g., ABSTRACT).

Applicant further argues that because Anklesaria teaches selection for neomycin, that the cells are a clonal subpopulation and not the cells the cells of Applicant's invention, and therefore they do not anticipate Applicant's claims (Applicant's arguments of 20 October 2004).

This argument is not persuasive because the pending claims do not have any such limitation that the cells are not particular subsets cells, and therefore, the claims would encompass the invention of Anklesaria. If Applicant wished to exclude any particular conditions or steps, such limitation may be added to the claims; however, such amendments to the claims may invite new rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 7, and 11 remain rejected, and Claims 19, 23, and 27 are rejected for reasons necessitated by the amendments, under 35 U.S.C. 103(a) as being unpatentable over Anklesaria

'87 as applied to Claims 1-2, 5-6, and 9-10 above, and further in view of U.S. Patent No. 5,635,386 to Palsson, et al., hereinafter referred to as "Palsson '386" for reasons of record in the previous Office Actions of 6 October 2003 and 19 May 2004.

Response to Arguments

Applicant's arguments filed 9 February 2004 have been fully considered but they are not persuasive.

Applicant argues that there exists (i) no suggestion or motivation to modify one of the references, or combine the two references; (ii) no reasonable expectation of success upon such combining or modification; and (iii) that the references do not teach all the limitations of the claims (Applicant's Response of 20 October 2004, p. 11, paragraphs 1-2).

Such arguments are not considered persuasive, in view of the Examiner's initial rejection, which provided motivation to modify Anklesaria's teachings with that of Palsson (Non-Final rejection of 6 October 2003, "Moreover, one of skill in the art at the time the invention was made would have been motivated to modify the teachings of Anklesaria '87 with that of Palsson '386, and use human cell lines in humans to obtain the benefit of rescuing humans exposed to radiation or enhance hematopoeisis", pp. 4-5), and a reasonable expectation of success upon such modification ("Furthermore, the artisan would have had a reasonable expectation of success, as bone marrow transplantation was already known and the cultures taught by Palsson '386 were known to afford improved methods for bone marrow transplantation, which necessarily demonstrates that cell lines themselves may be used in bone marrow transplantation in humans", Id.). Moreover, each of the references teaches all of the limitations of the claims (Id.).

Applicant argues that neither Anklesaria nor Palsson suggest to or motivate the skilled artisan to arrive at the presently claimed invention (Applicant's argument of 20 October 2004, p. 11, paragraph 3).

Such is not considered persuasive. As has been stated, Anklesaria teaches the use of marrow stromal cells to treat bone marrow ablation (e.g., Official Action of 15 June 2003, pp. 3-5). Moreover, Anklesaria specifically recognizes that a number of non-cell line derived marrow stromal cells have been used to reconstitute the same bone marrow ablation (p. 7681, paragraph bridging columns). Furthermore, Palsson provides the motivation to perform the same methods in humans with human cells, to obtain the benefit of rescuing humans with marrow ablation (e.g., Official Action of 6 October 2004, pp. 4-5).

Applicant argues that Ankelsaria teaches the administration of transformed cell lines, and that therefore, the references teach away from Applicant's claimed invention, which Applicant argues does not comprise such transformed cell lines (Applicant's response of 20 October 2004, pp. 11-12, paragraph bridging).

Such arguments are not persuasive, as the rejection is not based on the disclosure of the present application, but on the claims themselves, which encompass the cells of Anklesaria and/or Palsson, and do not require passage of cells for no more than three passages. Moreover, as stated in the prior rejections, the reason for the damage to the marrow is considered irrelevant to the claims, as the method is concerned with recovery, not with a method of damaging marrow (e.g., Office Action of 6 October 2003, pp. 3-4). Lastly, it is apparent from Anklesaria that total body irradiation results in an ablation of the marrow and subsequent lack of hematopoetic regeneration (Anklesaria, INTRODUCTION), and that is a primary reason for the studies of

Anklesaria, which shows recovery of the marrow after stromal cell engraftment (e.g., Official Action of 19 May 2004, p. 5, paragraph 3).

Applicant further argues that Anklesaria does not teach the cells described in the specification, and Palsson does not correct the deficiency, because Palsson does not mention the use of isolated marrow stromal cells cultured for no more than 3 passages as argued is described in the as-filed specification to be administered to a mammal for rescuing a mammal from total body irradiation (Applicant's argument of 20 October 2004, p. 12, paragraphs 2-3).

Such arguments are not persuasive because again, the rejection is based on the claims, not upon the specification. Moreover, the teachings of Anklesaria do encompass primary isolated marrow stromal cells, isolated from a mouse and administered allogenically (e.g., Office Action dated 6 October 2003, p. 4), and Palsson does teach that such cells may be used for treating humans (Id.). It is noted that the references are not each required, individually, to teach all the aspects of the claims, but the combination of the references must, under the aforementioned requirements, make obvious the claims. (e.g., Official Action of 19 May 2004, p. 6, paragraph 2)

Applicant further argues that the specification teaches the co-culturing of the stromal cells with hematopoeitic stem cells, and that armed with such teachings, Applicant's claims are not obvious or anticipated by either Anklesaria and/or Palsson (Applicant's argument of 20 October 2004, p. 12, paragraph 3).

Such arguments are not persuasive because again, the rejection is based on the claims, and not on the specification. As recited, Claims 3, 7, and 11 encompass only the following limitations:

Claim 3: administration of isolated marrow stromal cells from an allogenic donor to a human that has been irradiated, wherein the marrow stromal cells are administered immediately after isolation or after any period of *in vitro* culturing, wherein the cultured cells are primary marrow stromal cell cultured cells.

Claim 7: administration of isolated marrow stromal cells from an allogenic donor to a human, wherein the stromal cells are administered immediately upon isolation or after a period of *in vitro* culturing, wherein the cultured cells are primary marrow stromal cell cultured cells.

Claim 11: administration of isolated marrow stromal cells from an allogenic donor to an irradiated human, wherein the stromal cells are administered immediately upon isolation or after a period of *in vitro* culturing, wherein the cultured cells are primary marrow stromal cell cultured cells.

Hence, these cells can, optionally be cultured, by any method, for any period of time, and do not even need to be cultured. Moreover, marrow stromal cells are primary because they are derived from a mouse body (Ankelsaria, ABSTRACT). Such arguments have been substantively made in the previous official action of 19 May 2004, pp. 6-7).

Applicant argues that from reading Ankelsaria the skilled Artisan would only have a reasonable expectation of success for transformed/immortalized cell cultures (Applicant's response of 20 October 2004, p. 13, paragraph 1).

Such is not persuasive. Ankelsaria teaches that other have shown that marrow stromal cells, which are not disclosed as transformed or immortalized, have been shown to reconstitute marrow (p. 7681, paragraph bridging columns). Moreover, Palsson teaches such cells that were not transformed (Palsson, entire reference). Lastly, the Examiner has no reason to believe that

transformed/immortalized cells act are structurally different in some manner that would preclude them from working in the disclosed methods, especially considering the evidence to the contrary (Ankelsaria, p. 7681, paragraph bridging columns; Palsson, entire reference).

Applicant further argues that Palsson teaches the co-culturing of hematopoetic stem cells, and Anklesaria teaches neomycin-transformed and selected cells, and that, therefore, there would be no reasonable expectation of success for rescuing an animal from total body irradiation (Applicant's argument of 20 October 2004, p. 13, paragraph 2).

Such arguments are not considered persuasive because Anklesaria specifically teaches stromal cells encompassed by Applicant's claims being used for treating total body irradiation (INTRODUCTION). Again Palsson provides further evidence that such treatments can be similarly applied in the case of humans (Office Action dated 6 October 2003, pp. 4-5). Moreover, Palsson teaches "culturing human stem cells and/or human hematopoietic progenitor cells and/or human stromal cells in a liquid culture medium" (Palsson, ABSTRACT). Hence, Palsson is not even limited to co-culturing of cells. Lastly, Palsson is not the only reference, and Ankelsaria teaches the administration of primary marrow stromal cells themselves (Official Action of 15 June 2004, pp. 3-4 paragraph bridging).

Applicant makes an argument that the cited references do not teach or suggest all of the limitations of the claim limitations, arguing that Ankelsaria does not teach or suggest all of the claims defined by the specifcation, all the embodiments of the claims. Moreover, Applicant argues that Palsson does not overcome the deficiencies of Ankelsaria because Palsson teaches co-culturing of cells, and therefore teaches away from the claimed invention. (Applicant's response of 20 October 2004, pp. 13-14, paragraph bridging).

Such arguments are not considered persuasive. Neither Ankelsaria, Palsson, nor the combination of the references must teach all of the embodiments of the claims; they simply have to make obvious a single embodiment embraced by the claims. Moreover, Palsson is not limited to the co-culturing of cells (ABSTRACT). Lastly, as has been repeated throughout the prior official Actions, Ankelsaria and Palsson obviate all of the prior limitations to the claims, as well as the newly-presented limitation of primary cultured cells, because such stromal cells are primary cells, being derived from a mouse.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 21, 25, and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ankelsaria, et al. (1987) Proc. Natl. Acad. Sci., USA., 84: 7681-85 and U.S. Patent No. 5,635,386 to Palsson, et al., filed 2 November 1994, patented 3 June 1997, both of record.

The subject claims are drawn to methods of rescuing a mammal from a lethal does of total body irradiation, methods of enhancing hematopoiesis in a mammal, methods of enhancing hematopoietic stem cell differentiation in a mammal, methods of enhancing hematopoietic recovery in a mammal given a lethal dose of total body irradiation, methods of treating a mammal comprising an ablated marrow, methods of enhancing hematopoiesis in a mammal

comprising an ablated marrow, and methods of increasing survival of a mammal exposed to a lethal dose of total body irradiation, each method comprising the administration of isolated marrow stromal cells from an allogenic donor mammal to an irradiated mammal, thereby [performing the method], wherein said isolated marrow stromal cells are administered immediately upon isolation or following *in vitro* culturing for no more than the third passage.

As has been stated, the methods of damage to the marrow, if present, are not considered limiting, as the claims are drawn to recovery, or enhancing the hematopoeisis, of bone marrow, not with a method of damaging bone marrow (e.g., Official Action of 19 May 2004, p. 5, paragraph 3). Hence, these limitations are not considered limiting for purposes of art rejections.

Ankelsaria teaches engraftment of clonal bone marrow stromal cells *in vivo* and subsequent stimulation of hematopoeitic recovery (TITLE). Moreover, Ankelsaria teaches that non-cell-line marrow stromal cells have been shown to reconstitute marrow ablations in the past (p. 7681, paragraph bridging columns). However, Ankelsaria does not teach that such cells should be cultured for less than 3 passages. It is also noted that Ankelsaria leads the Artisan predicts that the reason certain infusions in the past have not worked is that the number of cells used for transplantation were inadequate (p. 7685, col. 1, paragraph 3).

On the other hand, Palsson teaches methods for regulating the specific lineages of cells produced in human hematopoeitic cell cultures (TITLE), with methods of culture, *inter alia*, primary marrow stromal cells, from humans (ABSTRACT). Moreover, one advantage of growing such cells in culture is to expand the number of cells available for infusion into the patient to have an adequate number of cells, necessarily implying that the number of passages

required would be a function of the number of cells donated and the number of cells required for adequate infusion (col. 3, paragraph 2).

Hence, it would have been obvious to modify the methods of Ankelsaria and use the human primary stromal cells of Palsson, passaged for 3 rounds. The Artisan would have been motivated to do so in those cases that 3 rounds of passage would allow for the growth of the requisite number of cells to produce the desired effect: increased hematopoeitic growth. Moreover, the Artisan would have had a reasonable expectation of success, as Ankelsaria had shown that such cells were capable of stimulating the hematopoeitic recovery in marrow, and Palsson had provided the methods for growing the marrow stromal cells, as well as the fact that both references had demonstrated the need, in certain instances, to obtain more cells for transplantation to be effective.

CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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